47

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/477,082	KIDD ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,11-16,29,48-51,54 and 56-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,11-16,29,48-51,54,56,58,60,61 and 63-65* is/are rejected.

7)☒ Claim(s) *57,59 and 62* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed Dec. 3, 2003 is acknowledged. Claims 27, 28, and 55 were canceled. Claims 63-65 were added.

Claims 2, 3, 11-16, 29, 48-51, 54, 56-65 are pending and examined on the merits.

Claim Rejections Withdrawn:

2. The rejection of claims 55 and 27-29, 58 and 59 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

3. The rejections of claims 27, 28 and 55 as anticipated by Hunter, Dixit, Wallach, or Alnemri are withdrawn in view of the cancellation of the claims.

4. The rejection of claim 56 as anticipated by Hunter or Dixit, or of 56, 57 and 60 as unpatentable over Dixit in view of Herman I and further in view of Herman II is withdrawn in view of the fact that neither Hunter nor Dixit teaches methods comprising the detection of methylation of CASP8 genomic DNA, and that Dixit fails to suggest methods comprising the detection of methylation of CASP8 genomic DNA.

5. The rejection of claim 51 and 11-15 as anticipated by Dixit is withdrawn in view of the fact that Dixit does not teach methods of diagnosis of cancer comprising the detection of

inactivation of CASP8 gene expression, wherein inactivation of CASP8 gene expression is indicative of the presence of cancer.

6. The rejection of claims 2, 3, 11-14, 48 and 51 under 35 U.S.C. 102(b) as being anticipated by Scaffidi (Scaffidi, C. et al, Journal of Biol. Chem., 272(43): 26953-26958, 1997, Oct.) is withdrawn upon consideration of new grounds of rejection.

7. The rejection of claims 2, 3, 11-14, 48 and 51 under 35 U.S.C. 102(a) as being anticipated by Juo (Juo, P. et al, Current Biol., 8: 1001-1008, 1998, Sep.) is withdrawn in view of the amendment.

8. The rejection of claims 2, 3, 48, 49, 50, and 54 under 35 U.S.C. 102(e) as being anticipated by Hunter (US Patent 6,172,190; January 9, 2001; effective filing date Feb. 27, 1997) is withdrawn in view of the amendment.

Claim Rejections Maintained:

9. The rejection of claims 2, 3, 48-50, and 54 under 35 U.S.C. 102(b) as being anticipated by Dixit (WO 97/46662; published 11 Dec. 1997) is maintained for the reasons of record.

Dixit teaches methods of detection of "apoptosis protease-7", which is also known as ICE LAP-7 or FLICE, which is another name for caspase-8. Dixit teaches assays of caspase-8 that comprise detecting the absence of CASP8 protein (see page 52, line 2- page 53, line4); and that

comprise detecting the absence of CASP8 mRNA (page 45, lines 1–18; page 48, lines 14-31). Thus, Dixit teaches methods that are the same as that claimed.

Applicant's arguments have been carefully considered, but are not persuasive. Applicants argue that Dixit fails to teach methods of detection of the absence of CASP8 protein or of CASP8 mRNA in a primary cancer cell. This is not found persuasive because Dixit teaches methods in tissue and fluid samples derived from patients, and specifically teaches cancer patients (page 46, lines 13-45).

New Grounds of Rejection:

10. Claims 48, 54, 2, 3, 49, 50, 63, 51, 11-14, 64, and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because of the phrases "detecting the absence of expression of a CASP8 protein" and "detecting the absence of a CASP8 mRNA". The specification provides no structural definition of CASP8 protein or of CASP8 mRNA. It is known in the art that the CASP8 gene may be transcribed into multiple splice variants (see Scaffidi, of record). Therefore, it is not clear if "detecting the absence of expression of a CASP8 protein" and "detecting the absence of a CASP8 mRNA" refers to method of detecting one of the mRNA species or one of the protein species and determining that the one species is not present, or if

absence of expression of a CASP8 protein" and "detecting the absence of a CASP8 mRNA" refers to a method of detecting all of the mRNA species or all of the protein species and determining that none of the species are present.

11. Claims 63, 51, 11, 12, 15, 16, 13, 14, 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of prognosis of neuroblastoma comprising the detection of methylation of CASP8 gene does not reasonably provide enablement for methods of diagnosis comprising the detection of methylation of CASP8 gene, or for methods or diagnosis or prognosis comprising the detection of the absence of "CASP8 protein" or "CASP8 mRNA". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The disclosure does not contain an adequate written description, examples, or guidance by which methods comprising the detection of "CASP8 protein" or "CASP8 mRNA" characterized only by the phrase "CASP8 protein" or "CASP8 mRNA" could be placed into the hands of the skilled artisan with a reasonable expectation of success without requiring undue experimentation for the following reasons.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The specification fails to define the scope of ""CASP8 protein" or "CASP8 mRNA". Therefore, the methods read on methods employing nucleic acids encoding variants of "CASP8 protein" or "CASP8 mRNA, such variants including, for example, deletions from, or insertions or substitutions of residues within "CASP8 protein" or "CASP8 mRNA. The prior art teaches

that CASP8 mRNA and CASP8 protein encompass several isoforms (see Scaffidi, C. et al, Journal of Biol. Chem., 272(43): 26953-26958, 1997, Oct.). The specification fails to teach an association of cancer with all, or a representative number of, CASP8 mRNA or CASP8 protein isoforms. Additionally, the specification fails to describe the structure of the mRNA species that is detected in the working examples; and the specification fails to describe the structure of the protein species that is detected by Western blot in the working examples. Thus, although the specification contains data demonstrating an association between neuroblastoma samples having MYC overexpression and CASP8 gene deletion or gene methylation, the specification fails to put into the hands of the skilled worker a method for the diagnosis or prognosis of cancer comprising the detection of any of the isoforms or all of the isoforms of caspase-8 mRNA or caspase-8 protein, or any of the possible products derived from mutations, deletions or insertions of the CASP8 gene. Without the teachings that relate specifically to methods for the detection of mRNA species and protein species, and to teachings directed to the relationship between detecting these species and the existence of or prognosis of cancer, one of skill in the art would have to conduct further undue experimentation.

The instant method claims encompass methods for the diagnosis or prognosis of all types of cancers. However, the specification only provides a working example demonstrating the gene methylation or a combination of gene methylation and gene deletion is associated with MYC overexpression in neuroblastoma cancer samples. The conclusions drawn from the data are that because MYC overexpression is an art-recognized indicator of poor prognosis in a number of cancers, that because CASP8 gene methylation alone or in combination with CASP8 gene deletion is associated with MYC overexpression in neuroblastoma, then CASP8 gene

methylation alone or in combination with CASP8 gene deletion is to be considered an indicator of poor prognosis in neuroblastoma cells. While the data appear to demonstrate that detection of CASP8 gene methylation alone or in combination with CASP8 gene deletion may be a useful indicator of poor prognosis for neuroblastoma, the data do not extrapolate to all other cancers. Furthermore, it is not clear how measurement of CASP8 gene methylation alone or in combination with CASP8 gene deletion would serve as a diagnostic method. The specification fails to teach what other possible diagnosis one of skill in the art would be differentiating from, and the specification fails to teach that CASP8 gene methylation alone or in combination with CASP8 gene deletion is found in any other cancer besides neuroblastoma. Further experimentation would be required of one of skill in the art for the practice of the full scope of the claimed invention, but because the diagnosis and prognosis of any and all cancers cannot be predicted from the results of one specific cancer, the finding of an association with another cancer would be merely fortuitous.

12. Claims 48, 54, 2, 3, 49, 50, 63, 51, 11, 12, 15, 16, 13, 14, 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the genus of "CASP8 mRNA" and genus of "CASP8 protein" is not adequately described because the specification fails to contain a written description of a sufficient number of the members of either genus. As discussed, above either genus encompasses a broad range of

chemical species because the prior art teaches that the CASP8 gene may be alternatively spliced to yield many isoforms, and also because, absent a definition in the specification, the terms "CASP8 mRNA" and "CASP8 protein" encompass any number of species resulting from insertions, deletions and mutations.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is for purposes of the 'written description' inquiry, "*whatever is now claimed" (*see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of "CASP8 mRNA" or "CASP8 protein" used in the method claims and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of manufacturing or testing the claimed process. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or testing it. One cannot describe what one has not conceived. See Fides v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112, is severable from its enablement provision. (See page 1115).

13. Claims 48, 54, 56, 60, 61, 63, 51, 11, 12, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detection of CASP8 genomic DNA methylation wherein the methylation is detected by methylation polymerase chain reaction (PCR) assay, does not reasonably provide enablement for any and all methods of detection of DNA methylation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is that the claimed methods are single means claims as described in MPEP 2164.08(a). See also In re Hyatt, 708 F.2d 712, 714-715, 218 USPQ 195, 197 (Fed. Cir. 1983).

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The claimed inventions are drawn to methods of detection CASP8 gene inactivation comprising the detection of CASP8 gene methylation. The claims do not recite method steps for performing the detection of gene methylation, and therefore covers every conceivable means for achieving the stated purpose. However, the specification teaches one means for the detection of CASP8 gene methylation, and fails to teach that any other methods exist or are known to the inventor. Therefore, one of skill in the art cannot practice the full scope of the claimed

invention, because further and undue experimentation would be required to discover other means of detecting CASP8 gene methylation.

14. Claims 48, 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mandruzatto (Mandruzzato, S. eta l. J. Exp. Med., 186(5): 785-793, 1997, Aug.).

The claimed inventions are drawn to methods for detecting inactivation of a CASP8 gene expression in a primary cancer cell, comprising performing on the cell an assay for detecting the absence of expression of a CASP8 protein.

Mandruzzatto teaches that a CASP8 gene mutation results in the mutation of one of the CASP8 alleles, producing a protein that impairs apoptosis in cells that have been transfected with the mutated allele (page 790, 1st to 2nd col, bridging para). Mandruzzato teaches that this mutation is present in primary tumor cells of the patient (page 789-790, bridging paragraph). Mandruzzato teaches that tumor cells from the patient express both the normal and the mutated allele, but that the mutation may be dominant because the mutation might result in the inability of the cancer cell to assemble the active tetramer of caspase-8 protein (page 790, 2nd col. 3rd complete para).

Mandruzzato fails to explicitly teach an assay comprising the detection of the absence of expression of a CASP8 protein. However, because Mandruzzato teaches that the mutation likely results in the inability of a cancer cell to form an active tetramer of caspase-8, and because the mutation appears to be a dominant mutation, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Mandruzzato to make a biochemical or immunological method for the detection of the absence

of a functional caspase-8 tetramer in a primary cancer cells as a measure of inactivation of the CASP8 gene.

15. Claims 48, 54, 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scaffidi (supra) in view of Mandruzatto (Mandruzzato, S. et al., J. Exp. Med., 186(5): 785-793, 1997, Aug.; cited in the IDS).

The claimed inventions are drawn to methods for detecting inactivation of a CASP8 gene expression in a primary cancer cell, comprising performing on the cell an assay for detecting the absence of expression of a CASP8 protein.

Scaffidi teaches that a small cell lung carcinoma cell line SCLC22H is negative for FLICE (caspase-8) expression (page 26955, 1st col., 1st full para). This was demonstrated by immunoblot with anti-FLICE monoclonal antibodies (Figure 2, page 26955). The absence of FLICE protein may be due to any of the reasons of claim 54, homozygous deletion, heterozygous deletion coupled with gene silencing by methylation, and homozygous gene silencing by methylation.

Scaffidi fails to teach this method using a primary cancer cell. However, Mandruzzato teaches that a partial or complete failure to transmit the signals of apoptosis transduced through caspase-8 may confer a selective advantage to tumor cells of patient BB49 (page 791, 1st col., 3rd full para). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Scaffidi for the measurement of caspase-8 protein in primary cancer cells to determine if CASP8 gene was inactivated leading to the lack of expression of caspase-8 protein. One of ordinary skill in the art would have had a

reasonable expectation of success in using the method of Scaffidi in a primary cancer cell, because Mandruzzato teaches that lack of caspase-8 expression likely confers a selective advantage on tumor cells.

16. Claims 29 and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by Boehringer Mannheim (Boehringer Mannheim, 1997 Biochemicals Catalog). Claims 29 and 58 are drawn to kits comprising primers for amplification of at least a part of the 5' untranslated region of CASP8 genomic DNA, wherein the primers are used in a methylation polymerase chain reaction (PCR) assay, or for the amplification of regions comprising SEQ ID NO: 1 or comprising SEQ ID NO: 2.

Claims 29 and 58 read on random hexamer mixtures of Boehringer Mannheim, because the primers are to be used for the amplification of at least a part of the 5' untranslated region or for amplification of sequences that comprise either SEQ ID NO: 1 or SEQ ID NO: 2. Therefore, Boehringer Mannheim teaches kits that are the same as that claimed.

Conclusion

No claim is allowed. Claims 57, 62 and 59 are objected to for depending from cancelled claims.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D. can be reached at (571) 272-0871.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
April 1, 2004

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